RESEARCH ARTICLE

Computational Comparison of the Stability of Iminium Ions and Salts from Enals and Pyrrolidine Derivatives (Aminocatalysts)

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Dedicated to Prof. Dr. Cesare Gennari on the occasion of his 70th birthday

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Abstract: The energies of CH_2=CH–CH=N^+R_2 + HNR*$_2$ → CH_2=CH–CH=N^+R*$_2$ + HNR_2 reactions (exchange of propenal between two secondary amines) and of similar equilibria with cinnamaldehyde have been calculated and compared. Iminium ions from pyrrolidines with substituents that can help stabilize the positive charge are especially stable in the gas phase, as expected, whereas in very polar solvents the predicted order of stability (of their iminium ions) is: *O-tert*-butyldiphenylsilylprolinol > pyrrolidine > *O*-methylprolinol > 2-*tert*-butyl-pyrrolidine > Jørgensen–Hayashi catalyst > 2-tritylpyrrolidine > *N,N*-dimethylprolinamide > trimethylsilyl prolinate > 3-triflamidopyrrolidine > methyl prolinate >> MacMillan-1 catalyst > MacMillan-2 catalyst. When ion pairs such as iminium tetrafluoroborates, in $CHCl_3$, are compared, the order is similar. These data can be used to predict which iminium salts may predominate when two or more secondary amines and appropriate acids are added to conjugated carbonyl compounds.

Introduction

In previous articles by our group, to gain insight into secondary amine-catalyzed reactions, we have experimentally and computationally compared the relative stabilities of series of enamines.[1] Some enamines are formed in such small amounts that are undetectable by ^{1}H NMR spectroscopy, even in appropriate solvents and in the presence of dehydrating agents. In these cases, DFT and post-HF calculations can provide valuable information. An excerpt for the case of enamines from cyclohexanone and azolidine derivatives is updated in Figure 1. It shows that some pyrrolidine derivatives have a higher tendency than pyrrolidine, **1**, to form the indicated enamine: the TBDPS derivative of prolinol, **8**, as well as other silylated prolinols not included in Figure 1 for simplicity, and tetrazolate anion **3'** (bioisostere of **3**). By contrast, as it is known from the beginnings of organocatalysis, famous aminocatalysts 12[2] and **13–14**,[3] so useful when the substrates are aldehydes and enals, respectively, hardly react with ketones, which may be explained by their position in Figure 1.

As it is also well known, iminium ions or salts are involved as crucial intermediates (highlighted in yellow in Schemes 1 and 2) in the aminocatalyzed reactions of many carbonyl compounds, since the hydrolysis[4,5] of iminium ions or salts is essential for the release of the catalyst (the secondary amine) and therefore for the chemical turnover. This is true for the reaction of electrophiles with chiral enamines (Scheme 1) and for the reaction of nucleophiles with chiral iminium ions (Michael-type additions summarized in Scheme 2, without including intermediate hemiaminals). In this last case, the formation of the initial iminium ions (eniminium ions) is obviously a key step.

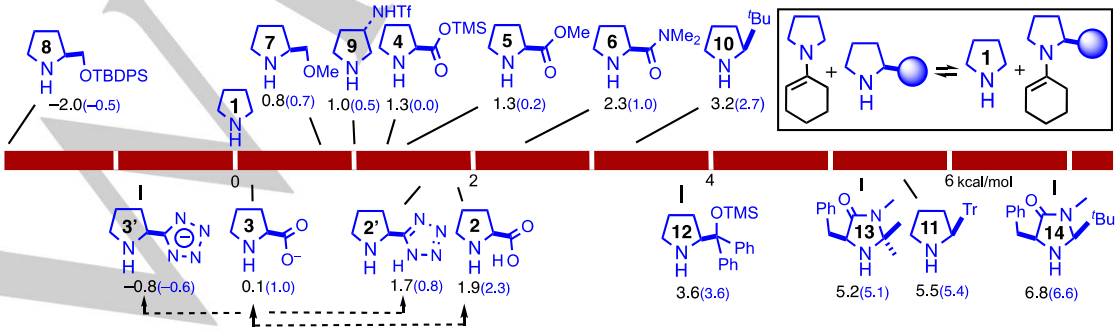
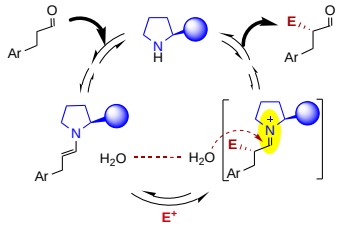
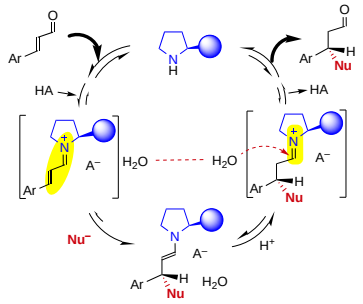


Figure 1. Comparison of total energies (Δ*E* values in kcal/mol) from M06-2X/6-311+G(d,p) calculations, for the formation of enamines from cyclohexanone, referred to its pyrrolidine enamine, in vacuum. Values within parentheses in blue belong to the equilibria optimized in M06-2X/6-311+G(d,p)·water/CPCM.



Scheme 1. Standard view of the organocatalytic reaction of carbonyl compounds, through chiral enamines, with electrophiles.



Scheme 2. Asymmetric Michael-type additions to enals, through chiral eniminium ions or salts.

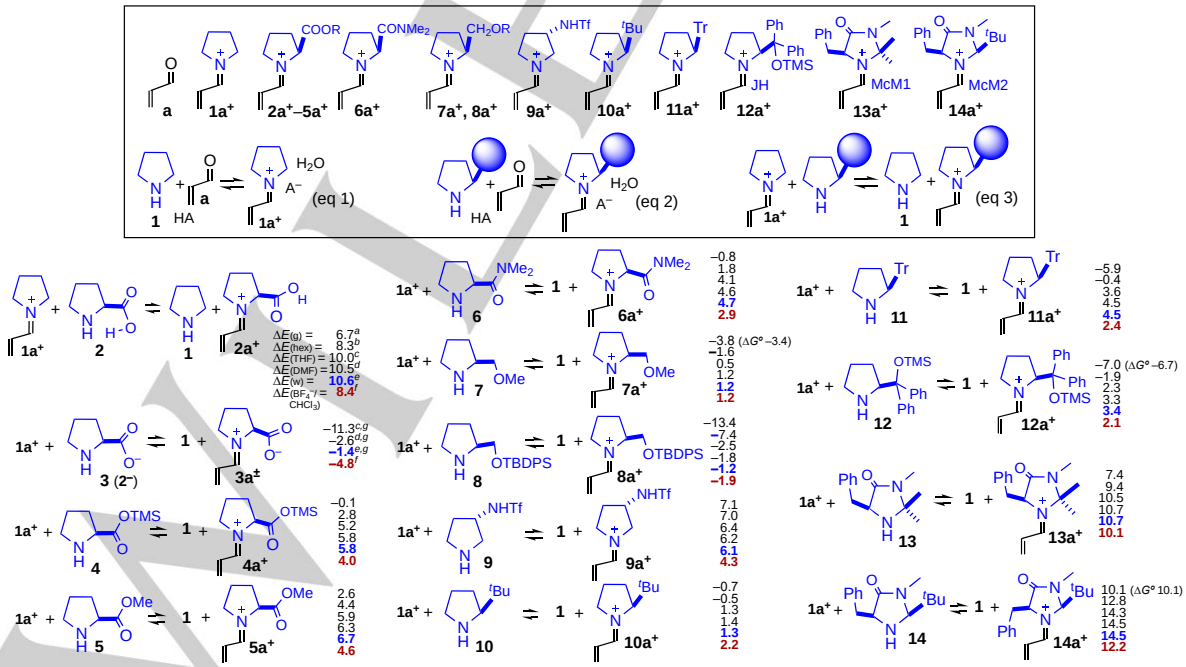
Thus, to gain insight into the energies of the iminium ions is complementary to our studies on the energies of enamines shown in Figure 1. In this regard, DFT calculations have been reported by the groups of Seebach,[6a-d] Mayr,[6e-h,7] Jörgensen,[6i,j] Houk,[6k–m] and others[6n–t] on iminium ions of secondary amines, mainly of the Jørgensen–Hayashi catalyst (JH, **12**) and of two MacMillan imidazolidinones (often abbreviated here as McM1, **13**, and McM2, **14**), and on mechanistic aspects of related organocatalytic reactions. It is worth noting that Seebach and coworkers[6c] characterized by NMR spectroscopy and X-ray analyses many of these eniminium salts, to note that, with few special exceptions, the *E*/*Z* ratios ranged from 88:12 to 98:2.[6c] Therefore, in the present work we have only calculated and compared the major *E* isomers. From a kinetic point of view, electrophilicity parameters were determined by Mayr and coworkers[6e] for a long series of cinnamaldehyde-derived iminium ions, including those from **12–14**. The same research group[6f] studied the effect of "derivatizing" the benzyl group (phenylmethyl group at the position 5 of **13**) on the conformer distribution and reactivity of the corresponding iminium ions; the experimental basicities and nucleophilicities of 32 pyrrolidine derivatives (including several MacMillan imidazolidinones) were also correlated.[6g]

As a complement to these and related studies,[6,7] we present here a comparison of the relative stability of iminium ions from various secondary amines. We will focus our attention on the iminium species arising from propenal (acrolein) and from (*E*)-3-phenylpropenal (cinnamaldehyde). The results may predict which eniminium ions, especially if two secondary amines are present, could be formed in larger concentrations, in different media. This may not be sufficient to predict the events in all cases, as the higher electrophilicity[7] of one eniminium salt may counteract its lower concentration but may throw light on the overall mechanism of the corresponding Michael addition.

Results and Discussion

Iminium ions from secondary amines and propenal

First, we examined the formation and hydrolysis—the direct and reverse reaction—of iminium ions from propenal (**a**), and specifically on the relative stability of a series of iminium ions (**1a**$^+$–**14a**$^+$) arising from pyrrolidine (**1**), chiral pyrrolidines (**2**–**12**), and chiral imidazolidin-4-ones (**13–14**). Scheme 3 shows the ΔE values for the exchange reaction between secondary amines and iminium ions, that is, for equation 3 (which is equal to eq 2 minus eq 1).



Scheme 3. Exchanges of propenal between pyrrolidine and analogs. Relative tendency, in kcal/mol, to afford iminium ions or their tetrafluoroborates: ΔE values, in kcal/mol, from the M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) total energies of the lowest energy conformers; representative ΔG^o values for the indicated exchanges within parentheses, also in kcal/mol. [a] Isolated species (gas, under vacuum). [b] In hexane/CPCM, single-point calculations (sp). [c] In THF/CPCM, sp. [d] In DMF/CPCM, sp. [e] In water/CPCM, sp (in blue). [f] Iminium tetrafluoroborates and the other species involved in the equilibrium optimized with M06-2X/6-311+G(d,p)·$CHCl_3$/CPCM (in red). [g] Geometries optimized in these media. TMS = trimethylsilyl. TBDPS = *tert*-butyldiphenylsilyl. Tf = trifluoromethanesulfonyl. Tr = trityl (triphenylmethyl).

These values come, of course, from the addition and subtraction of the total energies (*E*, in au) of the species involved in the equation, as obtained by the M06-2X method. In many cases, we have confirmed that for these exchanges, where the number of species is identical at the left and right side of the equation, the calculated ΔH^o values are practically identical to the corresponding ΔE values while the calculated ΔG^o values are quite similar to ΔE (differences between ΔE and ΔG^o are usually lower than 1 kcal/mol). A lot of computer time, at least for large species, is thus saved by comparing ΔE values. Positive values of ΔE thus indicate that the iminium ions from the 2-substituted pyrrolidine and analogs are thermodynamically less stable and, in this sense, more prone to hydrolysis than the iminium ion from pyrrolidine. Negative values, obviously, mean the reverse.

The presence of isolated cations in hexane, toluene, $CHCl_3$, or THF is not realistic. Iminium ions in DMF are likely to be solvated, but in water or aqueous solvents they will be immediately hydrolyzed, so the calculations in water as the implicit solvent are only indicative of the thermodynamic stability of these ions or their salts in a very polar solvent. However, what matters is to know how much the polarity of the solvents may stabilize such iminium ions in relation to the gas phase and nonpolar media. More realistic calculations, with ion pairs such as iminium tetrafluoroborates in $CHCl_3$, are also included in Scheme 3. To summarize, these energy values only suggest which eniminium ion or salt may eventually predominate if one enal is added to two or more secondary amines contained in the reaction flask (in the presence of a Brönsted acid).

The effect of solvents was estimated by means of CPCM (conductor-like polarized continuum model) and SMD calculations (solvent model based on density). The differences between DMF and water were generally minimal. DMF and water were thus considered together, to which we can add DMSO (see the Supporting Information), in the package of very polar solvents (either aprotic, mainly solvating cations, or protic, solvating both cations and anions).

Proline, because of the strong N···HOCO interaction (**2**), which in the solid state and very polar media leads to the zwitterionic form, is a particular case that has been analyzed with more detail in the Supporting Information. We suspect that, depending on the acidity of the medium, proline might show an intermediate behavior between **2** and its anion, **3**. To understand the case of proline (**2**) we calculated trimethylsilyl ester **4** and methyl ester **5**. With the arrangement of the proline COO group as depicted for **4** and **5** in Scheme 3, the three ΔE values were closer. However, we included in Scheme 3 and Figure 2 the outcome for the lowest energy minimum of a single molecule of **2**, with the above-mentioned internal hydrogen bond. This means a gain of energy, which causes the shift of the equilibrium to the left: the ΔE values for **2/2a**$^+$ are thus more positive than those for **4/4a**$^+$ and **5/5a**$^+$.

Figure 2, which graphically summarizes Scheme 3, shows the order of the relative stability to hydrolysis in different media of iminium ions **1a**$^+$–**14a**$^+$ and, in the last row, of their tetrafluoroborates.

Those catalysts on the left of pyrrolidine (top scale in Figure 2) are predicted to give rise to eniminium ions that are more stable than those of pyrrolidine, in the gas phase and in hexane. This occurs when the transfer of electronic density from a neighboring Ph, the electrostatic interaction with lone pairs of $OSiR_3$/OMe/$CONR_2$ groups, etc., can stabilize the delocalized cation (despite the opposite effect, against the formation of any iminium ion, expected for substituents containing electronegative atoms or EWGs). In this regard, the M06-2X method predicts that the stability of the main conformer of **8a**$^+$ is outstanding since, in addition to the electrostatic effect of the O electron pairs of OSi^tBuPh_2, the Ph groups play a significant role: whereas ΔE in the gas phase for the **8/8a**$^+$ pair is –13.4 kcal/mol, ΔE for OSi^tBuMe_2 (OTBS) is "only" –6.9 kcal/mol.

By contrast, in polar solvents or when ion pairs are considered (Figure 2, second and third rows), **1a**$^+$ becomes the thermodynamically more stable cation, relatively, with the exceptions of **8a**$^+$ and **3a**$^+$.

If two aminocatalysts were present in the medium, the species on the right side in Figure 2 would be present in lower concentrations (in accordance with $\Delta E \approx \Delta G^o \approx -1.36 \cdot \log K_{eq}$, in kcal/mol).

The fact that in very polar solvents most secondary amines examined here are found on the right to pyrrolidine deserves to be discussed. Apparently, a strong solvation produces a leveling effect, so the contribution of the above-mentioned stabilization factors decreases. Thus, five-membered rings with large substituents and/or with electron-withdrawing groups (EWGs) are found towards the right in Figure 2 (second and third rows). These iminium ions are predicted to be very prone to hydrolysis, from a thermodynamic point of view. This is not a handicap or an insurmountable limitation. For example, the tendency of MacMillan to give the corresponding iminium ions is lower than that of the other aminocatalysts of the list, a fact that is detrimental. However, if these ions can be formed in sufficient amounts under

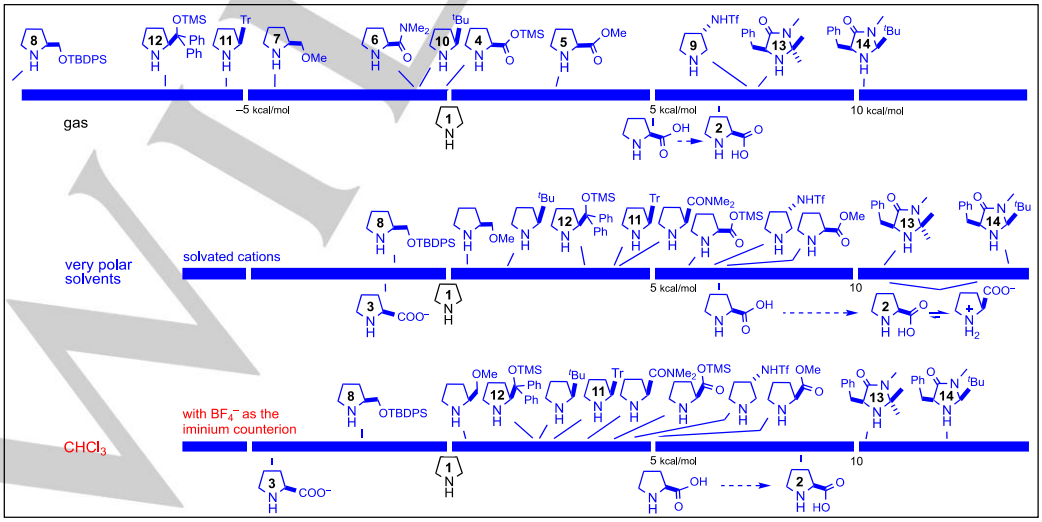
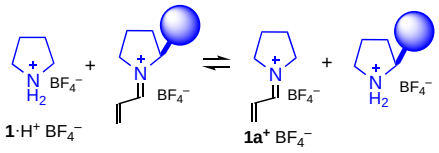


Figure 2. Comparison of ΔE values, in kcal/mol, from M06-2X energies for the formation of iminium ions **2a**$^+$–**14a**$^+$ in relation to that of **1a**$^+$, as well as for the formation of their iminium tetrafluoroborates (last row).

appropriate conditions, the heterocyclic moieties behave as strong EWGs, which is a positive factor for the attack of nucleophiles at positions $\beta/\delta/\zeta$ of propenal/pentadienal/heptatrienal derivatives.

Finally, if the catalyst is added as its ammonium salt, the equilibria to be compared could be those in Scheme 4 rather than those in Scheme 3. Scheme 4 would indicate the relative stabilities of eniminium ions with respect to the protonated forms of the catalysts (pyrrolidinium derivatives). However, these equilibria are hypothetical: partial deprotonation of the pyrrolidinium ions or some hydrolysis of the eniminium species must occur, otherwise they are not feasible in practice ("electrophiles or cations do not react with electrophiles or cations"). The calculated exchange energies for the equilibria shown in Scheme 4 (see the Supporting Information) are closer than those in Scheme 3. In general, there is a significant leveling off. For example, for the **1a**$^+$ BF_4^- + **14**·**H**$^+$ BF_4^- = **1**·**H**$^+$ BF_4^- + **14a**$^+$ BF_4^- reaction, ΔE = 3.4 kcal/mol (in $CHCl_3$), whereas ΔE = 12.2 for the **1a**$^+$ BF_4^- + **14** = **1** + **14a**$^+$ BF_4^- reaction (also in $CHCl_3$, see Scheme 3). An explanation is that the same electronic features of the substituents that stabilize or destabilize the eniminium ions can stabilize or destabilize the pyrrolidinium ions.



Scheme 4. Hypothetical equilibria in acid medium with exchange of a propenylidene group.

The cinnamaldehyde case

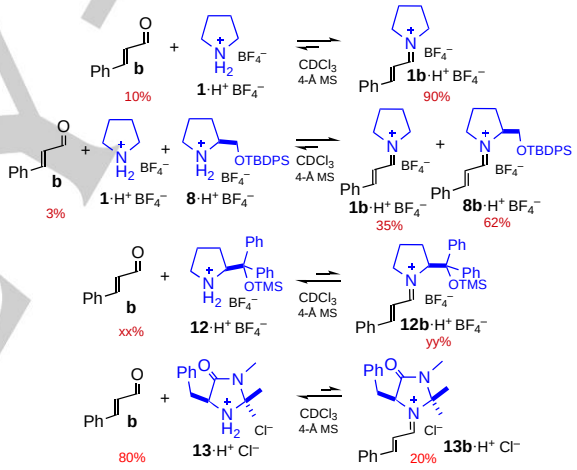
We repeated most of the preceding calculations with cinnamaldehyde (**b**) instead of propenal (**a**), to check whether more conjugated enals follow the same patterns or not. The results are collected in Scheme 5. They are parallel to those given in Scheme 3. Although there is often a leveling effect caused by the presence of the additional Ph group (in series **b**, with respect to series **a**), it is generally small.

The stabilization of cation **8b**$^+$ is worthy of mention, as it was the case of **8a**$^+$. The most stable conformer of **8b**$^+$ has the O atom of the OSi^{t}BuPh$_2$ (OTBDPS) pointing to the α-CH group, one of the Ph groups is over the CH=CH–Ph moiety, and the other over the pentagonal ring.

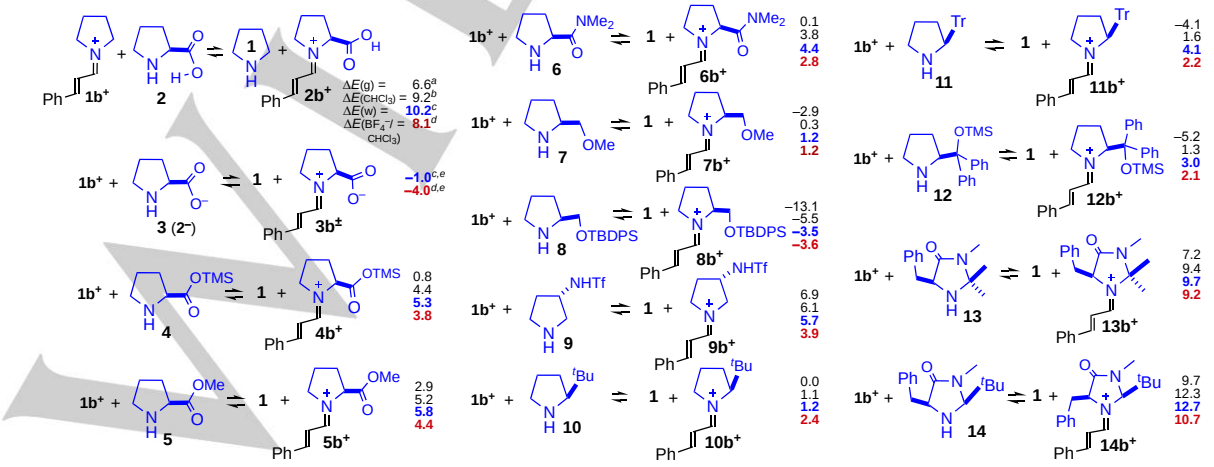
The stabilization of **12b**$^+$ by the OTMS group, under vacuum, is clear, as in the case of propenal (**12a**$^+$). Again, the leveling effect produced by the solvent polarity or by the counterion changes the equilibrium position. By contrast, **13b**$^+$ and **14b**$^+$ and their tetrafluoroborates are the most unstable members of the series, again.

Thus, Scheme 5 gives an idea of the approximate relative ratios in which the various iminium species may be found, if cinnamaldehyde and related enals were mixed, in the presence of an acid, with two or more aminocatalysts under equilibrium conditions, that is, in the absence of strong nucleophiles capable of participating in rapid Michael reactions or at low temperatures in which the added or formed nucleophilic species hardly react.

In practice, we mixed cinnamaldehyde (**b**) with representative pyrrolidinium or imidazolidinium salts (Scheme 6) in equimolar ratios, at room temperature. in the presence of molecular sieves. When the equilibria were reached (determined by taking aliquots), the NMR spectra indicated which iminium salts are preferably formed. Some competition experiments (1:1:1 equimolar mixtures of **b** and two protonated aminocatalysts) were also carried out. Scheme 6 summarizes the main results. For more examples and details, see the Supporting Information. …… …… …… …. … … …… ……



Scheme 6. Exemples of reactions of cinnamaldehyde (**b**) with equimolar amounts of pyrrolidinium salts in $CDCl_3$ and with two eniminium salts, as followed by ^{1}H NMR spectroscopy.



Scheme 5. Exchanges of cinnamaldehyde (**b**). [a] ΔE in kcal/mol from the M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) energies of the lowest energy conformers of the isolated species. [b] In $CHCl_3$/CPCM, single-point calculations. [c] In water/CPCM, sp. [d] M06-2X/6-311+G(d,p)·$CHCl_3$/CPCM, with BF_4^- as the counterion of the iminium ions.

Thermodynamics vs. kinetics

Nevertheless, also reasonably, as mentioned in the Introduction, the less stable eniminium ions or salts can be the more reactive electrophiles and vice versa. Although a full study of the kinetic aspects of these asymmetric reactions and/or the relative importance of thermodynamic and kinetic factors for all the species in Schemes 3 and 5 are outside the scope of this article (cf. the Supporting Information), the experimental results of Mayr et al.[7] confirm the above statement. For example, the reactivity of the following ion pairs in CH_2Cl_2 is **13b$^+$·TfO$^-$** > **12b$^+$·TfO$^-$** > **1b$^+$·TfO$^-$**, with relative k_2 values = 120:20:1 and 70:20:1, for the reactions with the TMS enolates of δ-valerolactone and γ-butyrolactone, respectively. Also, the order of reactivity is **14b$^+$·PF$_6^-$** > **13b$^+$·PF$_6^-$**, with relative k_2 values of 2:1 for the reaction in CH_3CN with piperidine, 4:1 with PPh_3, and 10:1 with the TMS enolate of γ-butyrolactone.[7]

Therefore, if two or more aminocatalysts of the series (**1**–**14**) were present in the reaction medium, the value of k_2 for the addition step of nucleophiles to **14b$^+$**, can partially compensate the relatively lower concentration of this cation (rate = k_2·[**14b$^+$**]·[Nu:] ∝ $e^{-\Delta G‡/RT}$·[**14b$^+$**]·[Nu:], see the Supporting Information for details).

Conclusion

The relative stabilities of iminium ions and salts from propenal or cinnamaldehyde and pyrrolidine and many related catalysts have been calculated and compared for the first time, in different media. Hence the effects of the substituents (on the five-membered ring of the catalysts) and the medium polarity have been quantitatively evaluated. Thus, the relative abundances of eniminium species involved in asymmetric Michael reactions can be estimated, which is particularly interesting if a bifunctional aminocatalyst or two or more aminocatalysts are present in the reaction medium. The two enals examined here may serve as references or models for other eniminium ions as well as for dieniminium and trieniminium ions.

In polar solvents, the iminium ion from pyrrolidine and propenal (**1a$^+$**) and that from pyrrolidine and cinnamaldehyde (**1b$^+$**) are predicted by the M06-2X method to be the most stable, with two clear exceptions. This is shown in Figure 3.

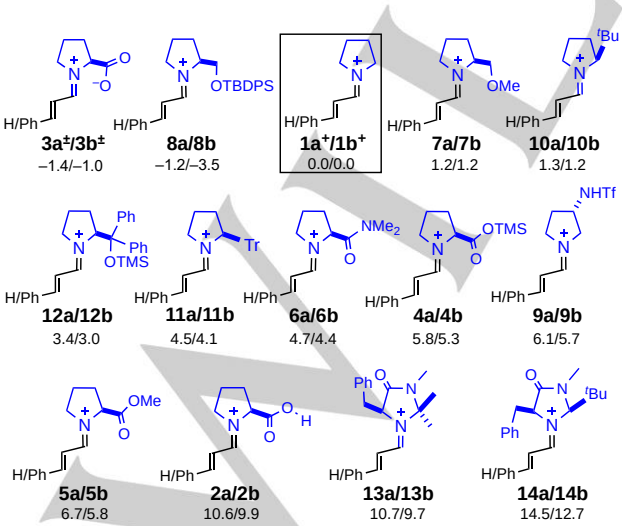


Figure 3. Summary of the relative stability of iminium ions **1a$^+$**–**14a$^+$** (1st value) and **1b$^+$**–**14b$^+$** (2nd value), in relation to their secondary amines, in very polar solvents (H_2O/DMSO/DMF, mean values in kcal/mol). Geometries optimized at the M06-2X/6-311+G(d,p)/CPCM level.

Scheme 3 summarizes the stability order of the solvated iminium ions investigated throughout this work, with respect to their amines. Iminium ions from MacMillan catalysts are among the less stable, that is, in the presence of other secondary amines they may be formed in very low concentrations, though this is (partially) compensated by their higher electrophilicity.

The results reported here may pave the way for the discovery or disclosure of true or additional dual aminocatalysis,[8] as well as for the future application of binary or ternary organocatalysis to domino or cascade reactions (as already developed for transition-metal catalysis). This can be based on the scales of the relative stabilities of the intermediate species shown in Figures 1–3 and Schemes 3 and 5, although further work will be required to expand the practical scope of these ideas and computational results.

Experimental Section

Computational methods. Calculations were carried out with the Gaussian 16 package[9] and with Spartan'20[10] (drawings also from Spartan). The M06-2X/6-311+G(d,p) method[11] was systematically used for the energy comparisons and all discussions are based on the results obtained with it, which is often abbreviated as M06-2X to save space in Figures and Schemes. Geometries were initially optimized for all the possible conformers of each species (usually a huge number) at the M06-2X/6-31G(d) level. Only the most stable *E* isomers and "all-*trans*" species were systematically calculated.

The effect of various solvents was estimated by optimization of the equilibrium geometries and total energies with implicit-solvent methods implemented in the above-mentioned packages. We mainly used the conductor-like polarizable continuum model (CPCM, Spartan'20) and the solvation model based on density (SMD, Gaussian 16). The total energy values were not identical, but the reaction energies were close to each other. The reasonable variation of the exchange energies depending on the features of substituents and solvents also confirm the reliability of the results. The ion pairs, with BF_4^- as the anion, were calculated with Spartan'20; the geometries were optimized at the M06-2X/6-311+G(d,p) level in $CHCl_3$/CPCM, after an extensive search of the low-energy minima with M06-2X/6-31G(d)·$CHCl_3$/CPCM. When the calculations at the M06-2X level of the main conformers gave close values for some of them, or when required to compare the reaction profiles corresponding to the Michael addition steps, we obtained the free enthalpies (Gibbs free energies, G) from the frequency calculations at the M06-2X/6-311+G(d,p) level with Gaussian 16 and/or with Spartan'20, with or without scaling factors for comparison (but no energy differences were observed).

NMR experiments. Representative reactions were followed by ^{1}H NMR spectroscopy, with the purpose of experimentally comparing the equilibrium positions predicted by calculations. Salts of some amino-catalysts examined in this work, either commercially available or simply prepared by addition of HBF_4·Et_2O to the secondary amines in THF or hexane, were dried under vacuum over P_4O_{10}, dissolved in $CDCl_3$ or in CD_3CN, and treated at room temperature with equimolar amounts of cinnamaldehyde (**b**) in the presence of 4-Å molecular sieves. The corresponding iminium salts are known compounds.[6c,12] The NMR spectra reproduced in the Supporting Information compare the ratios between the remaining **b** and the formed iminium tetrafluoroborates. Some 1:1:1 mixtures of **b** and two protonated aminocatalysts were also examined.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Chiral iminium ions · Iminium tetrafluoroborates · Organocatalysis · Asymmetric Michael reactions · M06-2X/6-311+G(d,p)-based predictions

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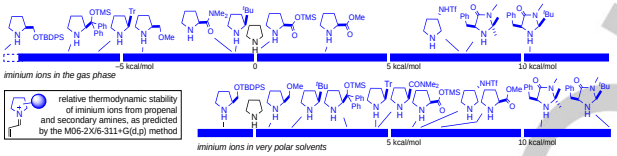

Formal exchange reactions between chiral secondary amines and iminium ions, as predicted by DFT calculations at the M06-2X level, are compared for the first time. The order of stability for these iminium species is thus established. The relative concentrations of the possible iminium ions in different media, if an enal is treated with two or more aminocatalysts, may be anticipated.

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